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British Journal of General Practice editorial: Which first-line antidepressant?

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Choice of first-line antidepressants for depression has been in the news over the past year, in relation both to NICE's on-line consultation on the proposed update of the 2009 NICE depression guideline [1], and the widely reported meta-analysis by Cipriani *et al* in the *Lancet,* comparing 21 antidepressants for efficacy and tolerability [2].

In its draft guidance for consultation, NICE recommends mirtazapine be considered a possible first-line antidepressant for more severe depression, alongside the selective serotonin reuptake inhibitors (SSRIs) [1]. This is new in 2018, as the 2009 guideline did not recommend mirtazapine first-line [3].

In a their network meta-analysis, Cipriani *et al* found that agomelatine, amitriptyline, escitalopram, mirtazapine, paroxetine, venlafaxine, and vortioxetine were more effective than other antidepressants [2]. They also found agomelatine, citalopram, escitalopram, fluoxetine, sertraline, and vortioxetine to be relatively more tolerable [2]. This suggests three antidepressants with higher

efficacy might be preferable first-line choices given their relatively high acceptability: escitalopram, agomelatine, and vortioxetine.

So should mirtazapine, escitalopram, agomelatine, and vortioxetine now be considered first-line for depression, along with the SSRIs?

Both the new NICE recommendation and the Cipriani conclusions are based on *network meta-analysis* (NMA): i.e. analysis in which multiple treatments are compared using both direct comparisons within randomised controlled trials, but also indirect comparisons across trials based on a common comparator. So, if antidepressants 'A' and 'C' have been compared to antidepressant 'B' in trials, you can infer how 'A' would perform compared to 'C' through the NMA, even if 'A' and 'C' have never been compared in the same trial. However, suggestions from NMAs that some antidepressants are more effective or more acceptable than others should be treated with caution, as their results are not always consistent with direct head-to-head comparisons. NMAs assume broad uniformity of studies and their participants and that optimal doses are always used. In reality none of these is true – further reason to treat outcomes with some suspicion.

In its first draft update in 2017, NICE recommended mirtazapine first-line for less severe depression as well as for more severe. This was because mirtazapine ranked relatively highly in an NMA of interventions when looking at reduction in depressive symptoms (response) as an outcome (although not when looking at 'remission' for which there was a lack of evidence), and was relatively cost-effective too [1]. However, the recommendation for first line use for less severe depression was removed following the first consultation, during which concerns were raised about safety of mirtazapine, arising from general practice prescribing database studies. In these studies, use of

mirtazapine was found to be associated with statistically significant absolute increases in rates of suicide and self-harm when compared with treatment with SSRIs and with no antidepressant treatment [4]. The updated draft NICE guidance acknowledges these risks but points out that observational studies cannot separate the effects of patients' underlying depression from any possible drug-related effect, especially as mirtazapine might preferentially be prescribed to patients with more severe depression. The full guidance states that the absolute increase in risk of suicide or self-harm for older people taking mirtazapine compared with those who did not take antidepressants was only 1.3%, and the recommendation of mirtazapine as an alternative to SSRIs for more severe depression remains [1].

Turning to escitalopram, 2018 is not the first time Cipriani and colleagues have suggested that it should be considered first-line due to a combination of higher efficacy and higher tolerability. A previous network meta-analysis by the same group published in 2009, comparing 12 antidepressants, stated that clinically important differences existed between antidepressants for both efficacy and acceptability, in favour of escitalopram and sertraline' [5]. Following the 2009 NMA, use of sertraline rose significantly while the use of citalopram levelled off, and that of fluoxetine fell [6]. However, escitalopram use did not increase significantly [6]. That may have been because of the relatively higher cost of escitalopram which was still under patent at that time, but since then its cost has fallen to a level similar to other more popular antidepressants [7].

So why not escitalopram first-line? One reason is concern about safety, as, like citalopram, it is known to prolong the electrocardiogram QTc interval, leading to an increased risk of arrhythmia in overdose, which led to a warning about its use from the Medicines and Healthcare Regulatory Agency (MHRA) in 2011. In contrast, sertraline has been shown to be safe when used in patients with cardiac problems, for example after myocardial infarction. Another reason is that the superior

efficacy of escitalopram has been demonstrated most convincingly in studies involving rats, not humans. In humans, pharmaceutical company funded direct comparisons have tended to use relatively low doses of SSRIs (e.g. sertraline 100-150mg) or serotonin-norepinephrine reuptake inhibitors (SNRIs) (e.g. venlafaxine 75-150mg) as comparators when testing efficacy, and relatively high doses of SSRIs (e.g. fluoxetine 60mg) as comparators when testing tolerability [8]. There is still a relative lack of direct head-to-head trial evidence for escitalopram's claimed superiority over other antidepressants, apart from citalopram [8].

Agomelatine is thought to act through a combination of antagonist activity at 5HT2C receptors and agonist activity at melatonergic MT1/MT2 receptors, which makes it unique among antidepressants, as it does not affect the reuptake of serotonin, norepinephrine (noradrenaline), or dopamine. A systematic review of direct head-to-head studies comparing it with standard antidepressants found it had similar efficacy to standard antidepressants, although published trials generally had more favourable results than unpublished studies [9]. Given a year's treatment costs £390 compared to £7 for fluoxetine, £9 for serotonin, £13 for escitalopram and £30 for citalopram [7], agomelatine should currently be limited to a third-line choice, but it is a viable alternative to other antidepressants when poor tolerability or contraindications preclude the use of SSRIs, SNRIs, and mirtazapine.

Vortioxetine is a serotonin transporter blocker which increases the extracellular concentration of serotonin, dopamine and noradrenaline, and so acts like an SNRI. A 2017 Cochrane review found no advantage when it was compared with SNRIs, being less effective than duloxetine, although it had less severe adverse effects [10]. The review criticised a relative lack of direct head-to-head comparisons between vortioxetine and the SSRIs, and the reliance placed on the results of NMAs to define its role [10]. Given a year's treatment costs £360, vortioxetine also should remain a third-line choice – as recommended by the NICE HTA of vortioxetine

So how should GPs choose a first-line antidepressant? Current NICE guidance [1, 3] and the British Association of Pharmacology (BAP) [11], suggest an SSRI should be considered first, unless there is a history of poor response or unacceptable side effects with SSRIs, in which case mirtazapine is an alternative if sedation and stimulation of appetite are desired effects, or else a tricyclic or tricyclic related drug such as nortriptyline or lofepramine if sedation is to be avoided. Older tricyclics should be reserved for when first-line treatment has failed, and monoamine oxidase inhibitors should only be prescribed by experts.

There are relatively few differences between SSRIs, although paroxetine is best avoided unless patients particularly ask for it, given its short half-life which leads to a greater risk of discontinuation symptoms, and its somewhat greater tendency to cause sexual dysfunction and weight gain. Sertraline is probably a safer choice than citalopram, escitalopram or fluoxetine in patients with heart disease particularly if overdose is a possibility, although it causes diarrhoea more often. Important interactions to beware include paroxetine attenuation of the benefits of tamoxifen; fluoxetine potentiation of the seizure risk with clozapine; and fluvoxamine potentiation of the effects of theophylline and clozapine, through inhibition of hepatic cytochrome P450 enzymes. Fluoxetine can also lead to serotonin syndrome when taken together with tramadol.

SSRIs as a class increase the risk of gastrointestinal, uterine and cerebral bleeding, particularly when taken with aspirin or non-steroidal anti-inflammatories, and so should be avoided by patients with dyspepsia, or given together with a protein pump inhibitor. They are also more likely to cause hyponatraemia especially for patients taking diuretics. For patients with these relative contraindications mirtazapine, nortriptyline or lofepramine would be a better first choice.

If patients have, in a prior episode of depression, tried SSRIs without response, mirtazapine or an SNRI would be a better first choice (venlafaxine or duloxetine rather than vortioxetine in the first instance). If they have had no response to previous treatment courses of SSRIs, mirtazapine and SNRIs, then agomelatine would be a reasonable choice.

The BAP guidelines state that useful pharmacogenetic predictors of response to antidepressants are not available, and that there is very limited evidence for any personal or family history being of use in predicting a differential response to different antidepressants, but that considering patients' preferences improves treatment adherence and may improve outcomes [11].

It should in any case be borne in mind that antidepressant treatment is best avoided if possible [12] and should only be prescribed if psychological interventions or exercise have either been tried first or are thought to be unsuitable, or if the patient has recurrent depression and is asking for drug treatment, or the patient is at risk of developing more severe depression (e.g. they have a history of severe depression).

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[7] Relative costs of antidepressants **DAVID or CHRIS – can you suggest the best reference to put in here please? The reference I used for the costs I've quoted is the Regional Drug and Therapeutics Centre, April 2018, at http://gmmmg.nhs.uk/docs/cost_comparison_charts.pdf**

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